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Proposed Registration Decision PRD2012-04

Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*)

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Overview

Proposed Registration Decision for Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*)

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of AgriPhage-CMM Technical and AgriPhage-CMM, containing bacteriophage to suppress bacterial stem canker on greenhouse tomatoes caused by *Clavibacter michiganensis* (subsp. *michiganensis*).

Additional data confirming efficacy of seedling treatment and hydroponic treatment against bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*) on greenhouse tomato would be required as a condition of full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of AgriPhage-CMM Technical and AgriPhage-CMM.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products A*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision4 on bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*)?

Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is the active ingredient in AgriPhage-CMM, which is a mixture of lytic bacteriophage strains highly specific to the causal pathogen of bacterial stem canker in tomato. The phage integrates its genome into the bacterial DNA, replicates rapidly within host cells and causes lysis of infected bacteria.

Health Considerations

Can approved uses of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) affect human health?

Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is unlikely to affect your health when AgriPhage-CMM is used according to the label directions.

People could be exposed to bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) when handling and applying AgriPhage-CMM. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (e.g., production of toxic byproducts);
- reports of any adverse incidents;
- its potential to cause disease or toxicity; and

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

By nature, bacteriophage are viruses that are only capable of infecting bacteria. Bacteriophage are not capable of infecting animals, plants, or fungi and are not capable of producing any toxins outside their hosts because they are not metabolically active. Bacteriophage rely on the bacterial host's metabolism for reproduction and survival. Bacteriophage themselves are not considered to be toxic. Also, since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will not alter the bacterial population in a way that could be harmful to humans. Although the relative exposure of people to bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) may increase from the use of AgriPhage-CMM, there have been no reports of adverse effects or incidents resulting from the direct exposure to naturally occurring bacteriophage.

Residues in water and food

Dietary risks from food and water are not of concern

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Bacteriophage, including bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), are common in nature and there have been no adverse effects attributed to dietary exposure to natural bacteriophage populations. Outside their host bacteria, bacteriophage are not toxic and are incapable of producing toxins. Furthermore, since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will not alter the bacterial population in a way that could be harmful to humans. Therefore, while the use of AgriPhage-CMM on greenhouse tomatoes will lead to transient increases in the population of bacteriophage over the short term, which could lead to an increase in dietary consumption, dietary risks are expected to be negligible. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent. The PMRA has determined that the establishment of an MRL is not required for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*).

Occupational risks from handling AgriPhage-CMM

Occupational risks are not of concern when AgriPhage-CMM is used according to label directions, which include protective measures

Growers handling AgriPhage-CMM can come into direct contact with bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) on the skin, in the eyes or by inhalation. For this reason, the product labels specify that growers exposed to this product must wear waterproof gloves, long-sleeved shirts, eye goggles, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks.

For the bystander, exposure is expected to be much less than that of handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What happens when bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) are introduced into the environment?

Environmental risks are not of concern

Following application, bacteriophage of *C. michiganensis* subsp. *michiganensis* is likely able to survive in the environment under favourable environmental conditions (i.e., low light, moist) but that over time populations of bacteriophage of *C. michiganensis* subsp. *michiganensis* are expected to return to natural background levels.

The effects of bacteriophage of *C. michiganensis* subsp. *michiganensis* on non-target organisms were considered. By nature, bacteriophage (phage) are only capable of infecting bacteria. Phage are not capable of infecting animals, plants, or fungi and are not capable of producing any toxins since they have no metabolism. Phage themselves are not considered to be toxic. Also, since *C. michiganensis* subsp. *michiganesis* does not produce toxins nor is it otherwise considered to be harmful to non-target organisms (other than tomato), the infection of these bacteria by bacteriophage of *C. michiganensis* subsp. *michiganensis* will not alter the bacterial population in a way that could be harmful to non-target organisms. Furthermore, minimal exposure to non-target organisms is anticipated from the use of AgriPhage-CMM to suppress *C. michiganensis* subsp. *michiganensis* in greenhouses.

Value Considerations

What is the value of AgriPhage-CMM?

Bacteriophage for *Clavibacter michiganensis* (subsp. *michiganensis*), the active ingredient in AgriPhage-CMM, suppresses bacterial stem canker caused by *Clavibacter michiganensis* (subsp. *michiganensis*) in greenhouse tomato.

AgriPhage-CMM can be applied for seedling treatment and hydroponic greenhouse treatment. AgriPhage-CMM is a novel pesticide and has a completely new mode of action, and offers an additional tool for managing bacterial stem canker, a destructive bacterial disease on greenhouse tomato. There are currently very few registered products for this disease. AgriPhage-CMM may be used as a component of an IPM strategy for bacterial stem canker on greenhouse tomato.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of AgriPhage-CMM to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As with all microbial pest control products, there are concerns with users developing allergic reactions through repeated high exposures to bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*). Therefore, anyone handling AgriPhage-CMM must wear waterproof gloves, long-sleeved shirts, eye goggles, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks. All early-entry workers to treated sites will be required to wear personal protection equipment until the spray has dried, including a NIOSH-approved respirator until spray mists have settled.

Environment

As a general precaution, the label prohibits the direct application of the product to aquatic habitats (such as lakes, streams and ponds). The label also directs growers to not allow effluent or run-off from greenhouses containing this product to enter lakes, streams, ponds or other waters and to avoid contaminating surface water by disposal of equipment wash waters.

Next Steps

Before making a final registration decision on bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*)

1.0 The Active Ingredient, its Properties and Uses

1.1 Identity of the Active Ingredient

Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) are a collection of bacterial viruses that have been isolated from the environment and are virulent to (i.e., infect and kill) *C. michiganensis* (subsp. *michiganensis*). If bacteriophage isolated by the registrant are shown to infect bacteria other than *C. michiganensis* or are shown to be temperate (i.e., able to integrate into the host bacterial genome) they are excluded from the collection of bacteriophage of *C. michiganensis* (subsp. *michiganensis*) used to prepare the technical product, AgriPhage-CMM Technical. Since the currently accepted taxonomic classification for bacteriophage using morphology is neither practical nor relevant to their use as an MPCA, the taxonomic classification of the host bacterium *C. michiganensis* is detailed below instead as it is most relevant to the identity of the MPCA.

Taxonomic designation of host bacterium[1]	
Kingdom	Bacteria
Phylum	Actinobacteria
Class	Actinobacteria
Sub-class	Actinobacteridae
Order	Actinomycetales
Sub-order	Micrococcineae
Family	Microbacteriaceae
Genus	*Clavibacter*
Species	*michiganensis*
Subspecies	*michiganensis*
Patent Status Information	No patents are held by the applicant in Canada.
Nominal purity of active	Technical grade active ingredient: 5.0×10^{10} plaque forming units (PFU)/g End-use product: 5.0×10^{10} PFU/g
Identity of relevant impurities of toxicological, environmental and/or significance	The technical grade active ingredient does not contain any impurities or micro contaminants known to be Toxic Substances management Policy (TSMP) Track 1 substances. The product is tested regularly to meet microbiological contaminants release standards. Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is not known to produce potentially toxic secondary metabolites.

[1] http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=28447

1.2 Physical and Chemical Properties of the Technical Grade Active Ingredient and the End-use Product

Technical Grade Active Ingredient – AgriPhage-CMM Technical

Physical state	liquid
Guarantee	5.0×10^{10} PFU/g (nominal)
Colour	golden yellow
Odour	none to slight
pH	5.3 – 6.2
Viscosity	0.90 cP at 21°C
Miscibility	completely miscible in water
Bulk Density	1.002 – 1.006 g/cc

End-Use Product – AgriPhage-CMM

Physical state	liquid
Guarantee	5.0×10^{10} PFU/g (nominal)
Colour	golden yellow
Odour	none to slight
pH	5.3 – 6.2
Viscosity	0.90 cP at 21°C
Miscibility	completely miscible in water
Bulk Density	1.002 – 1.006 g/cc

1.3 Directions for Use

AgriPhage-CMM is a bactericide used for the suppression of lytic bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*) on greenhouse tomato. AgriPhage-CMM may be applied as a foliar spray alone, in alternating spray programs or in tank mixes with other registered crop protection products. For maximum effectiveness, apply AgriPhage-CMM prior to or at the early onset of disease development or when conditions are conducive to heavy disease pressure. Thorough coverage and wetting of all foliage is essential for effective disease control.

1.4 Mode of Action

The active ingredient in AgriPhage-CMM is a mixture of bacteriophage strains for *Clavibacter michiganensis* subsp. *michiganensis*. Bacteriophages are highly specific obligate intracellular parasites that infect host bacteria by two possible routes once bacteriophages penetrate host cells: (1) they may either multiply in bacteria and kill the host cell at the end of the life cycle, or (2) the bacteriophages may enter a period of inactivity after which their DNA is incorporated into the bacterial DNA, which is passed on to succeeding generations of bacteria.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganism

The registrant utilizes restriction endonuclease analysis to identify and distinguish bacteriophage isolates in its collection of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*). DNA from bacteriophage is digested with either Bc11 or Stu1 enzyme then electrophoresed in 1% agarose gel. The bacteriophage are differentiable by distinctive banding patterns viewed under UV light after electrophoresed gels have been soaked in a solution of DNA-binding fluorescent dye.

2.2 Methods for Establishment of Purity of Seed Stock

Stocks of individual bacteriophage are stored at -80°C. Some bacteriophage isolates, however, are not stable at -80°C in which case the registrant stores them at 4°C. The bacteriophage are routinely verified to be virulent against *C. michiganensis* subsp. *michiganensis*. The identity of the host bacterium, *C. michiganensis* subsp. *michiganensis*, is further verified using a validated PCR method to detect a species-specific 614 base-pair fragment of DNA.

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The guarantee of AgriPhage-CMM Technical and AgriPhage-CMM is determined by applying serial dilutions of product on agar growth plates pre-inoculated with *C. michiganensis* subsp. *michiganensis*. The agar plates are then incubated allowing plaques (areas where bacteria have been lysed) to form. Plaques are counted and multiplied against the dilution factor giving a guarantee expressed as PFU (plaque forming units) per gram.

2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues that are expected to remain on food products, when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Bacteriophage, including bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), are ubiquitous in the environment and there have been no incidents of adverse effects attributed to dietary exposure to natural populations. Bacteriophage are not known to be toxic to humans or other mammals. Furthermore, since the host bacterium, *Clavibacter michiganensis* (subsp. *michiganensis*), does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will not alter the bacterial population in a way that could be harmful to humans. Therefore, while the use of AgriPhage-CMM in greenhouse tomato will lead to transient increases in the population of bacteriophage over the short term, which could lead to an increase in dietary consumption of this MPCA, dietary risks are negligible. Consequently, the PMRA has determined that setting an MRL is not required for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*). As a result, no methods to determine and quantify the residues of the MPCA are required.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of AgriPhage-CMM Technical and AgriPhage-CMM are acceptable.

Contamination by other microorganisms is monitored periodically using plate counts on agar growth media following standard microbiological methods. The product is not released for sale if contaminating microorganisms are detected.

2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism

Results from storage stability testing from two batches tested at different periods showed that the end-use product is stable for one year at 4°C.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

The PMRA conducted a detailed review of the toxicity and infectivity database for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), the active ingredient in AgriPhage-CMM Technical and AgriPhage-CMM. The database is considered complete, consisting of studies from the published scientific literature and rationales to waive test data requirements. Testing of the technical grade active ingredient is normally required to assess the health and safety of the form of the microorganism to be formulated for pesticidal purposes. The applicant submitted a rationale to waive all of the data requirements for the technical grade active ingredient (i.e., acute oral toxicity and infectivity, acute dermal toxicity and infectivity, acute pulmonary toxicity, acute intravenous infectivity, dermal irritation and reporting of hypersensitivity incidence). The scientific quality of the information submitted in lieu of actual test data is high, and the database is considered sufficient to characterize the infectivity and toxicity of this pest control agent and product.

The scientific rationale to waive the requirement for acute toxicity and infectivity testing of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is acceptable. Bacteriophage are not capable of infecting eukaryotic cells and are therefore not capable of being pathogenic to organisms other than their specific bacteria. Bacteriophage occupy the same niches as do their host bacteria. Humans are exposed to bacteriophage naturally through their own internal and external resident microflora. There are no known instances of toxicity from the direct exposure to bacteriophage and it is generally accepted that bacteriophage are not toxic to humans or other mammals. Based on the host specificity of bacteriophage, the potential toxicity or pathogenicity to humans from direct exposure to AgriPhage-CMM is negligible. Consequently, no further testing is required to assess the risk of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) to human health.

Even though the potential for adverse effects on humans from the use of bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is low, manufactured preparations of bacteriophage can pose their own unique hazards. These hazards are detailed below and their relevance to bacteriophage of *C. michiganensis* subsp. *michiganensis* discussed.

Bacterial toxins

When bacteriophage are manufactured in a bacterial host that is capable of producing toxic metabolites, there is the potential for these toxins to be present in the end-use product. In order to mitigate this risk, analytical methods must be employed by the manufacturer to confirm absence of toxins in the end-use product. Alternately, it could be shown that the bacterial host (identified to the strain level) is not capable of producing toxic metabolites.

Clavibacter michiganensis (subsp. *michiganensis*) is a well known, well characterized plant pathogen capable of infecting and causing disease in tomato (*Lycopersicon esculentum*). The entire genome of *C. michiganensis* subsp. *michiganensis* has been sequenced and analyzed. No toxin encoding genes have been identified. Furthermore, a search of the published scientific literature did not yield any publication indicating toxin production by *C. michiganensis*. AgriPhage-CMM is unlikely to contain contaminant bacterial toxins of concern to non-target organisms.

Genetic transduction

Bacteriophage are capable of tranducing genes from one host bacterium to another which occurs commonly in nature. If an ecological niche were inundated with bacteriophage, such as from the use of bacteriophage-based pest control products, then it is reasonable to expect that the susceptible bacterial populations would have an increased probability of genetic transduction. This effect could result in a greater probability of a bacterium acquiring a new trait which has the potential to pose a hazard to non-target organisms.

The *C. michiganensis* subsp. *michiganensis* genome has been sequenced and there are no genes of concern identified that could pose a hazard if transduction occurs between host bacteria. Furthermore, the host range of AgriPhage-CMM includes only *C. michiganensis*, further limiting the pool of genes available for transduction. The risk from genetic transduction within strains of *C. michiganensis* subsp. *michiganensis* to non-target organisms expected from the use of AgriPhage-CMM is negligible.

Lysogenic conversion

During infection of a host bacterial cell, all bacteriophage are capable of self-replicating, producing large numbers of virions which eventually leads to lysis of the host cell and release of new bacteriophage to the environment. Certain bacteriophage, called temperate bacteriophage, have the additional capability of inserting their genomes into their host bacterial genomes and reproducing and surviving along with their host. In this state it is also possible for the temperate bacteriophage to express some of its genes through the host. These are referred to as 'foreign' genes.

The ability of a temperate bacteriophage to express a foreign gene while infecting a bacterium could pose a hazard by modifying the phenotype of the host bacterium. The pathogenicity of the bacterium could be altered such that it has gained the ability to produce a toxic substance. The use of AgriPhage-CMM is unlikely to pose this hazard because temperate bacteriophage are excluded from use as an MPCA in the registrant's bacteriophage library (collection). The risk of lysogenic conversion to non-target organisms from the use of AgriPhage-CMM is therefore negligible.

Higher tier subchronic and chronic toxicity studies were also not required because of the expected low acute toxicity of the test substance and the inability of bacteriophage to infect eukaryotic cells.

Within the available published scientific literature, there are no reports that suggest bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) has the potential to cause adverse effects on the endocrine system of animals. Based on the weight of evidence of available data, no adverse effects to the endocrine or immune systems are anticipated from exposures to bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*).

3.2 Occupational / Bystander Exposure and Risk Assessment

3.2.1 Occupational

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary source of exposure to workers being dermal. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) are not capable of infecting humans, are not toxic, and are not capable of producing toxins. While there is no indication that AgriPhage-CMM is irritating to the skin or eyes, as a precaution in the absence of test data, it is considered a skin and eye irritant.

Although the overall risk to individuals exposed to large quantities of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is low, hypersensitivity reactions could develop upon repeated exposure to products containing AgriPhage-CMM. The PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions. Consequently, the signal words "Potential Sensitizer" and additional statements describing appropriate risk mitigation measures aimed at minimizing occupational exposures are required on the AgriPhage-CMM label.

Since AgriPhage-CMM is considered a skin and eye irritant, and a potential sensitizer, applicators and handlers are required to wear personal protective equipment, including waterproof gloves, long-sleeved shirts, long pants, eye goggles, NIOSH approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), shoes and socks. Early entry workers are required to wear a long-sleeved shirt, long pants, shoes plus socks and waterproof gloves until the spray has dried. Early-entry workers are also required to wear a NIOSH approved respirator with any N-95, R-95, P-95 or HE filter for biological products until spray mists have settled.

3.2.2 Bystander

Exposure to the general public is expected to be low based the proposed use of AgriPhage-CMM in greenhouses only. Overall the PMRA does not expect that bystander exposures will pose an unacceptable risk due to the low toxicity/infectivity profile for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) and the associated end-use product, AgriPhage-CMM.

The AgriPhage-CMM label does not allow applications to turf, residential or recreational areas; therefore, non-occupational dermal exposure and risk to adults, infants and children are low. Because the use sites are in greenhouses, exposure to infants and children in school, residential and daycare facilities is likely to be minimal to non-existent. Consequently, the health risk to infants and children is expected to be negligible.

3.3 Incident Reports Related to Human and Animal Health

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Health Canada website. Incidents from Canada and the United States were searched and reviewed for products containing bacteriophage for use as pesticides, including the USEPA registered product AgriPhage which contains the active ingredient Bacteriophage for *Xanthomonas campestris pv. vesicatoria* and *Pseudomonas syringae pv. tomato*. As of August 19, 2011, there were no health-related incident reports reported by the USEPA or the California Department of Pesticide Regulation ~~(CalDPR)~~, for end-use products containing this bacteriophage active ingredient.

3.4 Dietary Exposure and Risk Assessment

3.4.1 Food

AgriPhage-CMM is applied to greenhouse tomatoes up until the time of harvest; based on this timing of application, the proposed food use pattern could lead to a transient increase in the population of bacteriophage over the short term, which could in turn lead to an increase in dietary consumption. While the proposed use pattern may result in some dietary exposure with possible residues in or on agricultural commodities, negligible to no risk is expected for the general population, including infants and children or animals for the following reasons:

- Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is not toxic and is not capable of producing toxins;
- Bacteriophage, including bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), are common in nature with no adverse effects attributed to dietary exposure to natural populations; and,
- Since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will not alter the bacterial population in a way that could be harmful to humans.

Furthermore, higher tiered subchronic and chronic dietary exposure studies are not required because of the low toxicity of the MPCA. Therefore, there is no concern for chronic risks posed by dietary exposure of the general population and sensitive subpopulations, such as infants and children.

3.4.2 Drinking Water

No risks are expected from exposure to this microorganism via drinking water because exposure will be minimal and because bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is neither toxic nor pathogenic. When AgriPhage-CMM is used in greenhouses according to label instructions, the likelihood that bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will enter neighbouring aquatic environments is low. The AgriPhage-CMM label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also prohibited from allowing effluent or runoff from greenhouse facilities containing this product to enter lakes, streams, ponds or other waters. Furthermore, municipal treatment of drinking water is expected to remove the transfer of residues to drinking water.

3.4.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses and acceptable daily intakes are not usually possible for predicting acute and long term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing MPCAs is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (i.e., no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests. Based on all the available information, the PMRA concludes that bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is of low toxicity, is not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCA than the general population. Thus there are no threshold effects of concern and, as a result, no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of the MPCA, including neurological effects from pre- or post-natal exposures, and cumulative effects on infants and children of the MPCA and other registered microorganisms that have a common mechanism of toxicity, does not apply to this MPCA. As a result, the PMRA has not used a margin of exposure (safety) approach to assess the risks of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) to human health.

3.5 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain of food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as an MRL under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Bacteriophage, including bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*), are common in nature and there have been no adverse effects attributed to dietary exposure to natural bacteriophage populations. Outside their host bacteria, bacteriophage are not toxic and are incapable of producing toxins. Furthermore, since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) will not alter the bacterial population in a way that could be harmful to humans. While the use of AgriPhage-CMM on greenhouse tomato crops will lead to transient increases in the population of the MPCA over the short term which could lead to an increase in dietary consumption, dietary risks are expected to be negligible. Therefore, the establishment of an MRL is not required for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*).

3.6 Aggregate Exposure

Based on the toxicity and infectivity information submitted and other relevant information in the PMRA's files, there is reasonable certainty that no harm will result from aggregate exposure of residues of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) to the general Canadian population, including infants and children, when AgriPhage-CMM is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. Dermal and inhalation exposure to the general public will be very low since the product is to be applied in greenhouse sites only, and is not allowed for use on turf, residential or recreational areas. Furthermore, no adverse effects from exposure to other bacteriophage encountered in the environment have been reported. Even if there is an increase in exposure to this microorganism from the use of AgriPhage-CMM, there should not be any increase in potential human health risk.

3.7 Cumulative Effects

The PMRA has considered available information on the cumulative effects of such residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children. Besides naturally occurring bacteriophage in the environment, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with this active ingredient. No cumulative effects are anticipated if the residues of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) interact with natural populations of bacteriophage following application of AgriPhage-CMM.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate testing is intended to demonstrate whether an MPCA is capable of surviving or replicating in the environment to which it is applied, and could provide an indication of which non-target organisms may be exposed to the MPCA as well as provide an indication of the extent of exposure. Environmental fate data are not normally required for Tier I risk assessment

purposes and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing. Since no significant toxicological effects or other hazards to non-target organisms are expected from the greenhouse use of AgriPhage-CMM, no fate data are required to complete the environmental risk assessment of AgriPhage-CMM Technical and AgriPhage-CMM.

4.2 Effects on Non-Target Species

The PMRA conducted a detailed review of the environmental toxicology database for bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*). The database is considered complete, consisting of studies from the published scientific literature and rationales to waive test data requirements. Testing of the technical grade active ingredient is required to assess the environmental safety of the form of the microorganism to be formulated for pesticidal purposes. The applicant submitted a rationale to waive all of the environmental toxicology data requirements for the technical grade active ingredient (i.e., non-target organism tests including avian oral and pulmonary, freshwater fish, terrestrial arthropods, aquatic arthropods, non-arthropod invertebrates, terrestrial plants, and aquatic plants). The scientific quality of the information and data is high, and the database is considered sufficient to characterize the risk to non-target organisms of this pest control agent and product.

The scientific rationale to waive the requirement for toxicity and infectivity testing of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) was acceptable. Bacteriophage are not capable of infecting eukaryotic cells and are therefore not capable of being pathogenic to organisms other than their specific host bacteria. As bacteriophage are ubiquitous in the environment and occupy the same ecological niches as do their host bacteria, it is safe to assume that all non-target organisms have been exposed to bacteriophage at some time in their life cycle if not on a continuous basis. There are no known instances of toxicity from the direct exposure to bacteriophage and it is generally accepted that they are not toxic to non-target organisms. Based on the host specificity of bacteriophage, the potential toxicity or pathogenicity to non-target organisms from direct exposure to AgriPhage-CMM is negligible. Consequently, no further environmental testing is required to assess the risk of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) to non-target organisms.

Even though the potential for adverse effects on non-target organisms from the use of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is low, manufactured preparations of bacteriophage can pose their own unique hazards. These hazards are detailed below and their relevance to bacteriophage of *C. michiganensis* subsp. *michiganensis* discussed.

Bacterial toxins

When bacteriophage are manufactured in a bacterial host that is capable of producing toxic metabolites, there is the potential for these toxins to be present in the end-use product. In order to mitigate this risk, analytical methods must be employed by the manufacturer to confirm absence of toxins in the end-use product. Alternately, it could be shown that the bacterial host (identified to the strain level) is not capable of producing toxic metabolites.

Clavibacter michiganensis (subsp. *michiganensis*) is a well known, well characterized plant pathogen capable of infecting and causing disease in tomato (*Lycopersicon esculentum*). The entire genome of *C. michiganensis* (subsp. *michiganensis*) has been sequenced and analyzed. No toxin encoding genes have been identified. Furthermore, a search of the published scientific literature did not yield any publication indicating toxin production by *C. michiganensis*. AgriPhage-CMM is unlikely to contain contaminant bacterial toxins of concern to non-target organisms.

Genetic transduction

Bacteriophage are capable of tranducing genes from one host bacterium to another which occurs commonly in nature. If an ecological niche were inundated with bacteriophage, such as from the use of bacteriophage-based pest control products, then it is reasonable to expect that the susceptible bacterial populations would have an increased probability of genetic transduction. This effect could result in a greater probability of a bacterium acquiring a new trait which has the potential to pose a hazard to non-target organisms.

The *C. michiganensis* subsp. *michiganensis* genome has been sequenced and there are no genes of concern identified that could pose a hazard if transduction occurs between host bacteria. Furthermore, the host range of AgriPhage-CMM includes only *C. michiganensis*, further limiting the pool of genes available for transduction. The risk from genetic transduction within strains of *C. michiganensis* subsp. *michiganensis* to non-target organisms expected from the use of AgriPhage-CMM is negligible.

Lysogenic conversion

During infection of a host bacterial cell, all bacteriophage are capable of self-replicating, producing large numbers of virions which eventually leads to lysis of the host cell and release of new bacteriophage to the environment. Certain bacteriophage, called temperate bacteriophage, have the additional capability of inserting their genomes into their host bacterial genomes and reproducing and surviving along with their host. In this state it is also possible for the temperate phage to express some of its genes through the host. These are referred to as 'foreign' genes.

The ability of a temperate bacteriophage to express a foreign gene while infecting a bacterium could pose a hazard by modifying the phenotype of the host bacterium. The pathogenicity of the bacterium could be altered such that it has gained the ability to produce a toxic substance. The use of AgriPhage-CMM is unlikely to pose this hazard because temperate bacteriophage are excluded from use as an MPCA in the registrant's bacteriophage library. The risk of lysogenic conversion to non-target organisms from the use of AgriPhage-CMM is therefore negligible.

Higher tier non-target organism studies were not required because of the low acute toxicity of the test substance and the inability of phage to infect eukaryotic cells.

Based on a review of the published scientific data available on the effects of bacteriophage to non-target organisms, there is reasonable certainty that no harm will be caused to any group of non-target organisms from the use of AgriPhage-CMM. As a precautionary measure, however, standard pesticide label statements will prohibit handlers from contaminating aquatic habitats during application, clean-up and repair, as well as prohibit the effluent and run-off of treated greenhouses from entering lakes, streams, ponds or other waters.

4.3 Incident Reports related to the Environment

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/indexeng.php. Only incidents in which the pesticide is determined to be linked to the effects (Canadian causality of highly probable, probable and possible; U.S. causality of highly probable, probable and possible) are considered in the reviews. As of August 19, 2011, there were no environmental incidents reported in the PMRA Incident reporting database nor in the USEPA's Ecological Incident Information System for products containing bacteriophage for use as pesticides, including the USEPA registered product AgriPhage which contains the active ingredient Bacteriophage for *Xanhtomonas campestris pv. vesicatoria* and *Pseudomonas syringae pv. tomato*.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Suppression of bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*) for seedling treatment on greenhouse tomato

A total of five efficacy trials were submitted to evaluate the efficacy of AgriPhage-CMM on greenhouse tomatoes. Three of these trials were not reviewed, one Canadian trial was terminated by researchers due to extremely severe disease pressure and two US trials tested a different use

pattern. Two trials from Manitoba were reviewed for the control/suppression *Clavibacter michiganensis* (subsp. *michiganensis*) in greenhouse tomato. In both trials, sufficient disease pressure occurred where disease severity of 52 - 61% was observed 14 days after the tenth (last) application in the untreated-inoculated control. AgriPhage-CMM treatments at rates of 1.2 and 2.4 L/ha provided 38 - 58% reduction of bacterial canker control based on disease severity assessments in both trials. No significant differences were observed between the rates of 1.2 and 2.4 L/ha. Significantly lower disease control was shown in AgriPhage-CMM treatment at 0.6 L/ha during the course of applications. Under greenhouse conditions that are conducive to disease development, AgriPhage-CMM suppressed bacterial canker on tomato seedlings under low to moderate disease pressure.

5.1.1.2 Suppression of bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*) for hydroponic treatment on greenhouse tomato

The use of AgriPhage-CMM as foliar treatment on hydroponically grown greenhouse tomato was also proposed. In one of the trials, the treated seedlings were maintained for an additional period of time under typical practices employed in commercial greenhouses. No sufficient efficacy data were provided to support this use. However, a rationale extrapolating the rate for hydroponic greenhouse treatment (4 to 8 L per hectare) from the rates used for tomato seedlings was provided. Calculations were based on plant heights in the greenhouse compared to tomato seedlings in the efficacy trials. The claim is conditionally supported, pending an additional trial on hydroponic greenhouse treatment to confirm efficacy.

5.2 Phytotoxicity to Host Plants

There were no reports of phytotoxicity to the crops tested in any of the trials submitted.

5.3 Economics

No market analysis was done for this submission.

5.4 Sustainability

5.4.1 Survey of Alternatives

Refer to Appendix I, Table 1 for a summary of the active ingredients currently registered for the same uses as AgriPhage-CMM.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

The compatibility of bacteriophages with copper based formulations, Actigard 50WG and mancozeb products has been observed in efficacy trials where these products were alternated with bacteriophages in a program for the control of other bacterial diseases (e.g., bacterial spot and speck) in greenhouse tomato. Since copper compounds have been shown to reduce efficacy

of AgriPhage-CMM when they are applied at same time, copper products are recommended to be applied more than three days before the AgriPhage-CMM application in alternation with AgriPhage-CMM in a spray program. No deleterious effects on bacteriophages were reported when copper products are applied in this manner to manage bacterial diseases. There is sufficient evidence to conclude that AgriPhage-CMM is compatible with IPM practices used in the greenhouse tomato production in Canada.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

AgriPhage-CMM contains a mixture of bacteriophage strains that are highly specific to the causal pathogen of bacterial canker on greenhouse tomato. The probability of developing bacterial strains resistant to AgriPhage-CMM is considered low because of the use of strain mixtures.

5.4.4 Contribution to Risk Reduction and Sustainability

Some copper based fungicides/bactericides are currently registered for bacterial stem canker in tomatoes (either greenhouse or field) in Canada. However, the risk of phytotoxicity and crop injury, if applied at high temperatures, limit their use in the greenhouse. AgriPhage-CMM offers an additional tool to the Canadian greenhouse industry for managing bacterial stem canker in greenhouse tomatoes. It can be used in a spray program in alternation with copper products provided that copper products are applied more than three days before an AgriPhage-CMM treatment.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

AgriPhage-CMM Technical and AgriPhage-CMM were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5]

- AgriPhage-CMM Technical does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products.

- There are also no formulants, contaminants or impurities present in the end-use product, AgriPhage-CMM, that would meet the TSMP Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use product are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- AgriPhage-CMM Technical and AgriPhage-CMM do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and DIR2006-02.

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5 Regulatory Directive DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-11-30) pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613: *Part I Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 Notice of Intent NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act

8 Regulatory Directive DIR2006-02, *PMRA Formulants Policy*

7.0 Summary

7.1 Methods for Analysis of the Micro-organism as Manufactured

The product characterization data for AgriPhage-CMM Technical and AgriPhage-CMM were adequate to assess their potential human health and environmental risks. The technical grade active ingredient was fully characterized and the specifications were supported by batch analysis data. Storage stability data were sufficient to support a shelf life of one year at 4°C.

7.2 Human Health and Safety

The toxicity, infectivity, and other relevant information submitted in support of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) were determined to be sufficiently complete to permit a decision on registration. Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) are not pathogenic or infective to mammals, are not toxic, and are not capable of producing toxins. AgriPhage-CMM does not contain any toxicologically significant formulants.

When handled according to prescribed label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary source of exposure to workers being dermal and to a lesser extent inhalation. Precautionary statements on the AgriPhage-CMM label and the wearing of personal protective equipment by workers will adequately mitigate the risks from exposure. While bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is a potential sensitizer, inhalation and dermal exposure is not a concern if the required dust/mist filtering respirator and appropriate personal protective equipment stipulated on the product label are worn by handlers and applicators. Furthermore, precautionary labelling will alert users of the potential sensitization hazard of the product.

The health risk to general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is expected to be minimal since AgriPhage-CMM will only be applied to greenhouse tomatoes. The product is not to be applied to residential or recreational areas or to outdoor food or feed crops.

7.3 Environmental Risk

The scientific rationale and supporting published scientific literature submitted in support of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) were determined to be sufficiently complete to permit a decision on registration. Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is not capable of infecting organisms other than bacteria, specifically *C. michiganensis*, is not toxic and is not capable of producing toxins. Furthermore, environmental exposure to bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*) is expected to be minimal given that the use of AgriPhage-CMM is limited to greenhouses. The use of AgriPhage-CMM containing bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is not expected to pose an unacceptable risk to birds, mammals, arthropods, non-arthropod invertebrates, fish, plants and other microorganisms.

No additional studies were required to address the environmental fate and behaviour of bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*). Environmental fate data are higher tier requirements and are not normally required in the absence of significant toxicological effects in non-target organisms in Tier I testing.

As a general precaution, the AgriPhage-CMM label prohibits the direct application of AgriPhage-CMM to aquatic habitats (such as lakes, streams and ponds) and the release of greenhouse effluent and run-off to natural aquatic systems. The label also directs users to avoid contaminating surface water by disposal of equipment wash waters.

7.4 Value

Based on the efficacy data provided and information from published literature on bacteriophages, the use of AgriPhage-CMM has value in suppressing bacterial stem canker on greenhouse tomato. However, the evidence provided is not sufficient to fully support the claim as it was based only on two tomato seedling trials. Considering that AgriPhage-CMM is a novel pesticide and has a completely new mode of action, additional trials on greenhouse tomatoes are required in order to confirm the appropriate application rate.

A summary of the accepted uses for AgriPhage-CMM is presented in Appendix I, Table 2.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of AgriPhage-CMM Technical and AgriPhage-CMM, containing bacteriophage to suppress bacterial canker in greenhouse tomatoes caused by *Clavibacter michiganensis* (subsp. *michiganensis*).

Additional data confirming efficacy of seedling treatment and hydroponic treatment against bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*) on greenhouse tomato would be required as a condition of full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degree(s) Celsius
cc	cubic centimetre(s)
CMM	*Clavibacter michiganensis* (subsp. *michiganensis*)
cP	centipoise
DNA	deoxyribonucleic acid
g	gram(s)
ha	hectare(s)
IPM	integrated pest management
L	litre(s)
mL	millilitre(s)
MPCA	microbial pest control agent
MRL	maximum residue limit
NIOSH	National Institute for Occupational Safety and Health
PCPA	*Pest Control Products Act*
PCR	polymerase chain reaction
PFU	plaque forming unit
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Summary of alternatives for the same uses as AgriPhage-CMM

Crop	Disease	Active ingredient and FRAC fungicide group
Greenhouse tomato	Bacterial stem canker (*Clavibacter michiganensis* subsp. *michiganensis*)	Copper (M1)

Table 2 Use (label) claims proposed by applicant and accepted

Proposed claim	Accepted claim
Seedling Treatment: Use 1L of AgriPhage-CMM per 1000 square meters greenhouse space. Begin applications to seedlings (at the 4 leaf stage), immediately after planting or grafting, prior to or at early stages of disease development. Apply treatments daily. Use sufficient water to ensure complete coverage.	**Seedling Treatment:** **Rate:** 12 mL per 100 square meters greenhouse space. **Interval:** 3 - 4 days **Maximum application:** Ten applications can be used per crop cycle in the greenhouse. Use sufficient water to ensure complete coverage.
Hydroponic Greenhouse Treatment: Use 4 to 8 L of AgriPhage-CMM per hectare. Begin applications prior to or at early stages of disease development and continue throughout the growing season. Begin at the lower rate when plants are small, as plants increase in size, increase rate to ensure adequate coverage. Repeat application 1-3 times per week. Use sufficient water to ensure complete coverage Recommended dilution at 1000 liters of water per hectare.	**Hydroponic Greenhouse Treatment:** **Rate:** 40 mL per 100 square meters greenhouse space. **Interval:** 3 - 4 days Use sufficient water to ensure complete coverage.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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1771124 2009, AgriPhage-CMM product chemistry information, DACO: M2.9.1, M2.9.2, M2.9.3, M2.10.2, M2.10.3, M12.7 CBI

1771126 2008, Host specificity checks, DACO: M2.9.1, M2.9.2, M2.9.3, M2.10.2, M2.10.3, M12.7 CBI

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3.0 Environment

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